alpha-carbon coordinates. The distance of each eluted peptide from its hull was then computed (d: distance of peptide to protein surface) and normalized against the distance from the center of the hull (S: percent submergence in source protein). In our preliminary survey, 53% of the samples had d-values of 1A or less, with 51% having S-values of less that 15%, indicating that peptides that are selected as MHCII binders are relatively near the surface of their undigested source proteins. Our preliminary results indicate that timing, as well as affinity, may be equally important in MHCII binding.

3305-Pos Board B410

A Multiscale Approach for Path Sampling

Hiroshi Fujisaki, Motoyuki Shiga, Akinori Kidera.

Proteins often accompany conformational changes when they function in cells, and its characterization is one of the most important subjects in biophysics. The ability of theoretical and computational methods based on molecular dynamics simulations has been increasing due to the advance of hardware and algorithms, it is, however, still not feasible to simulate and clarify a biological role of conformational changes of (large) proteins. To address this time-scale problem from a different point of view, we proposed to use a statistical approach based on the Onsager-Machlup (OM) action [J. Chem. Phys. 132 (2010) 134101], where a path, not a configuration, is the most fundamental object to be studied, and its probability distribution is described by a path-integral representation using the OM action in the exponent. In the present study, we apply this formalism to a model polymer system considered by Micheletti and coworkers [J. Chem. Phys. 129 (2008) 074105], where they used the OM action to estimate the free energy landscape and the diffusion coefficient of a coarse-grained variable (end-to-end distance). We execute path sampling for the same model polymer with an Asakura-Oosawa-type interaction, and address some practical issues of path sampling when we apply it to a molecular system. We further discuss how coarse-grained variables can be used to accelerate the convergence of path sampling.

3306-Pos Board B411

In Silico Investigation of a Missense Mutation in CLIC2 Associated with Intellectual Disability

Shawn Witham, Kyoko Takano, Charles Schwartz, Emil Alexov.

While numerous nsSNPs (nonsynonomous SNP) have been reported in the CLIC2 gene in healthy individuals (indicating that the CLIC2 protein can tolerate amino acid substitutions while still being fully functional), we recently identified a missense mutation in CLIC2 on Xq28 in a male with X-linked intellectual disability (XLID). This mutation, c.303C>G (p.H101Q), was not observed in 1059 control X chromosomes, which indicates that it may contribute to intellectual disability. To test the possibility that p.H101Q is a disease-causing mutation, we performed extensive in silico simulations to calculate the effects caused by the p.H101Q mutation on CLIC2 stability, dynamics, and ionization states. We then compared the effects obtained for the (presumably) harmless nsSNPs. In silico analysis predicted that p.H101Q, in contrast with other nsSNPs, (a) reduces the flexibility of the joint loop which is important for the normal function of CLIC2, (b) makes the overall 3D structure of CLIC2 more stable and thus reduces the possibility of the large conformational change expected to occur from the soluble to membrane state of CLIC2, and (c) removes the positively charged residue, H101, from the joint loop which may be important for the membrane association of CLIC2. The results of the in silico modeling, in conjunction with the polymorphism analysis, suggest that p.H101Q is indeed a disease-causing mutation, which is the first one found in the family of the CLIC proteins. This work was supported by awards from NLM/NIH, grant numbers 1R03LM009748 and 1R03LM009748-S1.

3307-Pos Board B412

Automation of the Charmm General Force Field for Drug-Like Molecules

Kenno Vanommeslaeghe, Jayeeta Ghosh, Narendra K. Polani, Michael Sheetz, Sudhakar V. Pamidighantam, John W.D. Connolly, Alexander D. MacKerell Jr.

The CHARMM Force Field[1] is widely used for the study of biological macromolecules. Recently, we released the CHARMM General Force Field (CGenFF) which allows simulating drug-like molecules in an environment represented by the CHARMM biomolecular force field.[2] To facilitate the use of CGenFF, a computer program was developed that automatically assigns atom types, bonded parameters and charges to any organic molecule. The atom typing is rule-based and programmable, making it easy to update the atom typing scheme as the force field grows. Assignment of bonded parameters is based on substituting atom types in the definition of the parameter, and returns a ''penalty score'' as a measure for the accuracy of the approximation. Charges are assigned using an extended bond-charge increment scheme that should be able to capture short- and medium-range inductive and mesomeric effects.[3] This functionality is accessible on the web, which makes it possible to apply CGenFF on arbitrary molecules in a matter of seconds.[4] Although the program should ideally accept any molecule, the quality of the resulting parameters (as indicated by their ''penalty scores'') varies depending on whether a similar compound has been parametrized before. Therefore, an effort has been started to build a computational engine with the capability of automatically validating and/or optimizing parameters for drug-like model compounds of the user's interest in the framework of CGenFF, thus providing high-quality force field parameters for computer-aided drug design.[4]

1. A. D. MacKerell et al., J. Phys. Chem. B 1998, 102, 3586-3616
2. K. Vanommeslaeghe et al., J. Comput. Chem. 2010, 31, 671-690
3. K. Vanommeslaeghe et al., in preparation
4. NSF Award #0823198; https://www.paramchem.org/

3308-Pos Board B413

From Small Molecules to Macromolecules: Progress Towards a Charmm Drude Polarizable Force Field for the Nucleic Acids

Christopher M. Baker, Alexander D. MacKerell Jr.

Electrostatic interactions play a crucial role in determining the structure and function of biomolecules, and an important aspect of the electrostatic interaction is polarizability, the response of the molecular dipoles to an external electric field. Towards development of a comprehensive force field for biomolecules, initial work on the CHARMM Drude polarizable force field for nucleic acids focused on optimizing the theoretical model and developing parameters for small molecule analogs of the sugar, phosphate and base moieties.

With parameters for the small molecule analogs now in place, current work is focused on construction of the full nucleic acids, and details of this work will be presented here. Initial simulations of the full nucleic acids have demonstrated that the polarizable model is both robust and stable, and work is now underway to assemble the small molecule building blocks into the full nucleic acids. This procedure requires careful optimization of the parameters associated with covalent connections between the constituent moieties. Following initial optimization of the intramolecular connections, multiple simulations will be performed to provide a detailed assessment of macromolecular properties in comparison to experimental data. These results will be used to identify and correct any weaknesses in the force field, and are also an essential tool for validation of the model in condensed phase environments; they will give new insights into the importance of polarizability in nucleic acid simulations.

3309-Pos Board B414

Solid-State NMR Ensemble Dynamics as a Mediator between Experiment and Simulation

Taehoon Kim, Sunhwan Jo, Wonpil Im.

Solid-state NMR (SSNMR) is a powerful technique to describe the orientation of membrane proteins and peptides in their native membrane bilayer environments. Various SSNMR observables such as ^{2}H NMR quadrupolar splitting (DQS), ^{15}N chemical shift (CS), and ^{1}H-^{15}N dipolar coupling (DC) have been used to characterize the orientation of transmembrane (TM) helices with a static rigid-body model. In particular, TM helix orientational information is often related to membrane protein function and has been used to investigate the role of hydrophobic mismatch between TM helix and lipid bilayer. However, dynamic information of these TM helices can be missing or misinterpreted when a static model is used. We have investigated the orientation and dynamics of WALP23 in DMPC and GWALP23 in DLPC by determining ensemble of structures using multiple conformer models with various SSNMR restraint (DQS, CS, and DC) potentials. The resulting ensemble structures that satisfy the SSNMR observables are compared with those from MD simulations and free energy calculations in both explicit and implicit membrane. The good agreement illustrates that SSNMR-ensemble dynamics provides a means to extract the dynamic information from the SSNMR measurements and realistic explanation of the discrepancy between MD simulation and experimental interpretation based on a static model.

3310-Pos Board B415

An Integrative Approach using Numerical Models to Bridge Spatiotemporal Interactions of Subcellular Processes: Cell Spreading

Yannick Loosli, Reto Luginbuehl, Jess Snedeker.

After an initial phase of non-specific interactions with an adhesive substrate, cells enter a rapid phase of spreading. During this phase, unstable entities (focal complexes -FXs- and actin bundles) selectively mature into long lasting focal adhesions and associated actin stress-fibers. This process is regulated by complex signaling cascades involving mechano-sensation at the focal adhesions, and relies on the spatial and temporal coordination of a many proteins. This complexity presents a hurdle in elucidating the relationship between local stimuli and resultant global cellular behavior. Actual models have generally employed elaborate algorithms with many degrees of freedom precluding any insight into the modeled system behavior.

We propose an alternative modeling framework that drastically reduces the number of parameters by integrating discrete subcellular processes into a framework of weakly coupled functional modules. Module interaction is governed by few rules. In the case of cell spreading, we model the stochastic formation of FXs by discrete modules representing lamellipodial and filopodial activity, and consider the spatiotemporal interactions of these modules. These interactions are regulated by the top-level cellular objective. More specifically, maturation of nascent FXs and accompanying stress-fibers recruitment is driven by actin bundle bridging of overly-large distances between consecutive adhesions and the eventual spatial incorporation of stable filopodia by the lamellipodia. Based on this framework, an iterative and non-deterministic numerical algorithm was developed that enabled prediction of spread cell morphology (focal adhesion and stress-fiber layout), in a time dependent manner. Numerical outcomes were compared to a wide range of experimental evidence. For all tested substrates, the model provided robust replication of the experimental analog. We interpret this fact to imply that the selected functional modules and governing top-levels rules for their interaction were adequate to describe cell spreading.

3311-Pos Board B416

Developing a Fast Polarizable Force Field for Biophysical Simulations

George Kaminski.

Computer simulations have become very helpful in biophysical studies. It has been demonstrated by our and other groups that explicit treatment of the electrostatic polarization is crucial for obtaining biochemically accurate computational data in a variety of cases. For example, we have managed to calculate pKa values for protein residues within 0.6 - 0.7 pH units of the available experimental data. We have also shown that some experimentally known protein-ligand complexes have to be modeled with explicit polarization in order to reproduce the very existence of the complexes. Our results also allow to conclude that simulation of complexes with the Cu+ ion can have a ca. three-fold error in the magnitudes of the binding energies if the polarization is not included. We are now developing a complete polarizable force field for proteins using the second-order approximation formalism which permits to increase the computational speed by ca. an order of magnitude. Results of this ongoing development will be presented, and a number of relevant issues (including the relative importance of quantum mechanical and experimental data in fitting of torsional parameters) will be discussed.

3312-Pos Board B417

Compartmental Analysis of Intravaginal HIV Transport and Neutralization by Microbicides

David F. Katz, Jason A. Chen.

Microbicides are topically acting molecules intended to inhibit HIV-transmission by acting within luminal fluids and/or vaginal mucosa. Gels are a promising microbicide delivery modality, with clinical evidence that they can reduce the rate of sexually-transmitted HIV in women (Karim et al, 2010). We created a model of interacting vaginal co-transport of HIV virions and gel-introduced microbicides in four compartments: semen, gel, vaginal fluid, mucosa. Imaging studies of gel distribution have shown that mucosal surfaces has incomplete gel coating; there can be substantial surface area directly exposed to semen. HIV and microbicide transport occur by diffusion and convection, the latter modeled using Taylor dispersion theory. Here, the active microbicide is an HIV entry inhibitor that must collide with virions in sufficient numbers before they arrive at the mucosal surface to prevent transmission. Key model output is the time-dependent number of non-neutralized virions arriving at the tissue surface. Key inputs are: fraction of surface with coating; coating thickness distribution; viral load in semen; microbicide concentration in gel; parameters of HIV neutralization mechanism; HIV and microbicide diffusion coefficients in gel, semen and vaginal fluid; and time interval between gel application and semen deposition. Results show that infectious HIV transport to tissue is largely over uncoated regions, since HIV diffusion in gel is significantly restricted (Lai et al, 2010). If fractional coated area $>90\%$, most reasonable combinations of system parameters cause substantial HIV neutralization, with small numbers (~ 1000) of still-infectious virions reaching tissue. Lower fractional coated areas and increased HIV diffusion coefficients result in increased flux of infectious virions to tissue in a multivariate manner delineated by the model. This modeling helps improve our understanding of how HIV transmission can be reduced by rationally designed microbicides. [Support: NIH AI077289 and Duke CFAR].

3313-Pos Board B418

Deriving Effective Force and Moment due to Pairwise Interactions in Coarse Grain Simulations

Mohammad Poursina, Kurt S. Anderson, Jeremy Laflin.

We extend the approach used to approximate the long range gravitational force and the associated moments in spacecraft dynamics to calculate the pairwise forces in coarse grain simulations. First, we provide a relatively accurate approximation of the resultant force applied from an atom $\boldsymbol{P}$ to a rigidified superatom. Since this resultant force does not generally act through the center of mass of the superatom, it creates a moment about the center of mass of the body. This potentially valuable moment is completely neglected in bead model representations. We also calculate this moment which is very useful when the equations of motion are formed in articulated multibody-based framework. In this process, assuming each superatom as a discontinuous rigid body, we introduce the concept of the pseudointertia dyadic $\boldsymbol{I}_{\alpha}$. If the governing force field is the gravitational force, this pseudoinertia tensor represents the inertia matrix of the rigid body or system of particles. We show that the resultant force and moment applied to the superatom only depend on the location of the center of mass of the superatom with respect to the atom $\boldsymbol{P}$, and the pseudointertia tensor of the body. This tensor is calculated for each rigid domain of the system before starting the simulation; therefore, there is no cost associated with this tensor during the course of the simulation. Then, based on the results obtained in the previous step, we calculate the resultant force and moments between two rigid pseudoatoms due to the pairwise interactions among the individual atoms belonging to one superatom and the other one. We show that the resultant force and moments are functions of the relative location of the centers of mass of the bodies, and the pseudoinertia dyadic of the individual pseudoatoms.

3314-Pos Board B419

Relationship of the 2′-Hydroxyl Orientation in RNA to Watson-Crick Base Pair Opening

Elizabeth Denning, U. Deva Priyakumar, Alexander D. MacKerell Jr.

RNA molecules are one of the more versatile macromolecules within a cell as they have a variety of structures and functions. Thus, it is important when studying RNA using empirical force fields, to consider the models and methodologies used to study RNA, including the quality of force field parameters. CHARMM27 force field parameters exhibits Watson-Crick (WC) basepair opening in RNA molecules. Here, we present a series of new RNA force field parameters that improve the behavior of RNA molecules. The updates result in changes in the distribution of the 2'-hydroxyl torsion leading to a reduction the frequency and extent of WC base-opening events. As a result of the shift in the 2′-hydroxyl distribution, we observe results that are in improved agreement with experimental and RNA survey data. The optimal force field parameter was applied to study the behavior and folding mechanisms of different types of RNA molecules.

3315-Pos Board B420

Development of the Charmm Polarizable Force Field for Polypeptides Based on Drude Oscillators

Pedro E.M. Lopes, Xiao Zhu, Albert Lau, Benoit Roux,
Alexander D. MacKerell Jr.*.

Ongoing developments of polarizable CHARMM force field for proteins, based on the classical Drude oscillator, are presented. Inclusion of polarizability has the potential to describe physical properties of complex systems in a way not possible with current additive force fields. However, polarizable force fields are extremely sensitive to the environment and extreme care has to to be used in their development. For example, small changes of the electrostatic parameters result in large variations of the calculated properties relative to the reference QM values. In this work we describe the steps in optimization of the force field. The bonded parameters were developed based on the reproduction of QM and crystal structures and vibrational spectra of small models (ex. NMA, alanine dipeptide and proline dipeptide). Determination of the crucial electrostatic parameters was based on reproduction of QM electrostatic properties, dipole and quadrupole moments, of small (NMA and alanine dipeptide) and larger models (alanine 5-mer polypeptide) in different conformations. Determination of the electrostactic parameters pose a considerable challenge since ultimately, they have to be able to describe the electrostatic properties of small and extended compounds (ex. polypeptides) alike. VdW parameters were developed following the customary reproduction of condensed phase results (heats of vaporization and free energies of hydration). Finally, adjustments needed to fine tune the agreement between calculated and target properties of larger polypeptides are described.

3316-Pos Board B421

No New Islet Formation after Neonatal Islet Fission

Junghyo Jo, German Kilimnik, Abraham Kim, Manami Hara, Vipul Periwal.

Glucose homeostasis is regulated by the islets of Langerhans, a cluster of microorgans embedded in the exocrine pancreas. These pancreatic islets range in size from a few to several thousand endocrine cells independent of species over a range of body sizes, suggesting an optimal functional size. Humans have more but not larger islets than mice. To examine the developmental processes that produce this size range of islets, we used a novel method that images all the islets in an intact pancreas of the transgenic mice expressing a fluorescent protein specifically in beta cells. Based on changes of the islet size distribution from postnatal day 1 to week 20, we analyzed islet developmental processes such as birth, growth and fission with mathematical modeling. No new islets were formed after postnatal week 3. At early postnatal days, islet growth was size-dependent with more active cell